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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/619,359	STOCKER ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-10,12 and 14-38* is/are pending in the application.

4a) Of the above claim(s) *7,8,10,12 and 14-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7-14-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 5-10, 12, 14-38 are currently pending and are present for examination. Claims 5-6 and 9 are now under consideration. Claims 7-8, 10, 12, 14-38 remain withdrawn from consideration being drawn to non-elected invention.

Election/Restrictions

Applicant's election without traverse of Group I, claims 5-6 and 9 in the reply filed on 7-19-06 is acknowledged.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that applicant fails to provide appropriate SEQ ID NO for sequences depicted on p37 of the specification. See particularly 37 CFR 1.821(d).

Specification

Examiner notes that applicants have not updated the relationship of the instant application to its parent application that has matured in to a US patent. Examiner urges applicants to amend said information by providing the US patent number in response to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 and claims 6 and 9 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 is very confusing to the Examiner. Claim 5 is drawn to a polypeptide or a fragment thereof which comprises at least one amino acid of a P-glycoprotein selected from a group of amino acids of SEQ ID NO:2 and few amino acids of SEQ ID NO:4. The following points are not clear to the Examiner. It is not clear a)whether the amino acids of SEQ ID NO:2 need to be at the very same position in the isolated P-glycoprotein; b) whether the isolated polypeptide must comprise the amino acids of both SEQ ID NO:2 and SEQ ID NO:4 and if at the very same positions or any position. If the amino acids need to occupy the very same position then which amino acid is preferred at position 95, because it is common between SEQ ID NO:2 and SEQ ID NO:4. Also not clear is what specific function will the isolated polypeptide or its fragment have. It is also not clear whether the isolated polypeptide should have all the amino acids i.e., amino acid at position 93, 94 and 95 of SEQ ID NO:4 or can comprise any one amino acid selected from the group consisting of amino acids 93-95 of SEQ ID NO:4. Examiner requests clarification for all the above.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 recites the phrase "selected from the group of SEQ ID NO:5 and 6". It is not clear as to what applicants mean by the above phrase. It appears that applicants intended to

recite "selected from the group consisting of SEQ ID NO:5 and 6". If that were so amending the claim accordingly would overcome this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-6 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a P-glycoprotein comprising the full length amino acid sequence of SEQ ID NO:2, 4 or 5 or 6, does not reasonably provide enablement for any polypeptides or fragments thereof comprising at least one amino acid selected from the group consisting of amino acids 12, 24, 30, 74, 78, 86, 89, 90, 91, 92, 95, 97, 99, 102, 103, 104, 185,324, 363, 518, 635,650, 656, 659, 677, 730, 738, 742, 745,761,765,835,851,921,967, 1003, 1027, 1038, 1048, 1103, 1128, 1168 and 1277 of SEQ ID NO:2 and amino acids 93, 94 and 95 of SEQ ID NO:4 and having any function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 5-6 and 9 are so broad as to encompass any variant, mutant or recombinant P-glycoprotein comprising at least one amino acid selected from the group consisting of amino acids 12, 24, 30, 74, 78, 86, 89, 90, 91, 92, 95, 97, 99, 102, 103, 104, 185,324, 363, 518, 635,650, 656, 659, 677, 730, 738, 742, 745,761,765,835,851,921,967, 1003, 1027, 1038, 1048, 1103, 1128, 1168 and 1277 of SEQ ID NO:2 and amino acids 93, 94 and 95 of SEQ ID NO:4. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide amino acid sequence of only SEQ ID NO:2, 4, 5 or 6. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification is limited to teaching the use of full length SEQ ID NO:2, 4, 5-6 as a P-glycoprotein but provides no guidance with regard to the making of variants and mutants or with regard to other uses as claimed. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), the claimed invention would require undue experimentation. As

such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While polypeptide/enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any P-glycoprotein polypeptide comprising at least one amino acid selected from the group consisting of amino acids 12, 24, 30, 74, 78, 86, 89, 90, 91, 92, 95, 97, 99, 102, 103, 104, 185,324, 363, 518, 635,650, 656, 659, 677, 730, 738, 742, 745,761,765,835,851,921,967, 1003, 1027, 1038, 1048, 1103, 1128, 1168 and 1277 of SEQ ID NO:2 and amino acids 93, 94 and 95 of SEQ ID NO:4 because the specification does not establish: (A) regions of the P-glycoprotein structure which may be modified without affecting its original activity; (B) the general tolerance of P-glycoprotein to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in a given polypeptide with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polypeptides with an enormous number of amino acid modifications of the SEQ ID NOS:2, 4,5-6. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 5-6 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 5-6 and 9 are directed to a genus of polypeptides and their fragments, wherein said polypeptides comprise at least one amino acid selected from the group consisting of amino acids 12, 24, 30, 74, 78, 86, 89, 90, 91, 92, 95, 97, 99, 102, 103, 104, 185,324, 363, 518, 635,650, 656, 659, 677, 730, 738, 742, 745,761,765,835,851,921,967, 1003, 1027, 1038, 1048, 1103, 1128, 1168 and 1277 of SEQ ID NO:2 and amino acids 93, 94 and 95 of SEQ ID NO:4. Claims 5-6, 9 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides derived from SEQ ID NO:2, 4, 5 or 6 including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in the above sequences that have not been disclosed in the specification. No description has been provided of the polypeptide sequences encompassed by the claim. No

information, beyond the characterization of SEQ ID NO:2, 4, 5-6 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the function of all the polypeptide sequences derived from SEQ ID NO:2,4, 5-6 including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of functions. Therefore many functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 5-6 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 5-6 and 9 are directed to a genus of polypeptides and their fragments, wherein said polypeptides comprise at least one amino acid selected from the group consisting of amino acids 12, 24, 30, 74, 78, 86, 89, 90, 91, 92, 95, 97, 99, 102, 103, 104, 185,324, 363, 518, 635,650, 656, 659, 677, 730, 738, 742, 745,761,765,835,851,921,967, 1003, 1027, 1038, 1048, 1103, 1128, 1168 and 1277 of SEQ ID NO:2 and amino acids 93, 94 and 95 of SEQ ID NO:4. Claims 5-6, 9 are rejected under this section of 35 USC 112 because the claims are directed to a

genus of polypeptides derived from SEQ ID NO:2, 4, 5 or 6 including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in the above sequences that have not been disclosed in the specification. The specification does not contain any disclosure of the full structure of all sequences included in the claimed genera. The genus of polypeptides claimed is a large variable genus with the potentiality of having many different structures. Therefore, many structurally distinct polypeptides are encompassed within the scope of these claims. The specification discloses the full structure of only SEQ ID NO:2, 4, 5-6 of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. A sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by full length sequence or a recitation of structural features common to members of the genus, **which features constitute a substantial portion of the genus**. The recited structural feature of the genus (i.e., polypeptide comprising a at least one amino acid of SEQ ID NO:2 or 4 and fragments thereof) does not constitute a substantial portion of the genus as the remainder of the structure of P-glycoprotein polypeptide is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 5 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Veen HW et al. (GenBank Accession No. AAW44073, 6-26-1998) or Chen et al. (GenBank Accession No. A34914, 1995) or Devine et al. (GenBank Accession No. A38696, 1992) or Devault et al. (GenBank Accession No.A34786, 7-13-1990). This rejection is based upon the public availability of printed publications. Claims 5 and 9 of the instant application are drawn to

an isolated polypeptide (P-glycoprotein or MDRP-1a) or fragment thereof which comprises at least one amino acid of a cynomologous P-glycoprotein selected from the group consisting of amino acids 12, 24, 30, 74, 78, 86, 89, 90, 91, 92, 95, 97, 99, 102, 103, 104, 185,324, 363, 518, 535, 650, 656, 659, 677, 730, 738, 742, 745,761,765,835,851,921,967, 1003, 1027, 1038, 1048, 1103, 1128, 1168 and 1277 of SEQ ID NO:2 or comprising amino acids 93, 94 and 95 of SEQ ID NO:4, wherein the P-glycoprotein is identical to a human P-glycoprotein except for the at least one amino acid of a cynomologous P-glycoprotein. All the above references disclose such a polypeptide wherein said reference polypeptide comprises at least one of the above amino acids from either SEQ ID NO:2 or 4. Therefore, claims 5 and 9 are anticipated as written. (see enclosed sequence alignments)

Claims 5 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Veen HW et al. (GenBank Accession No. AAW44073, 6-26-1998) or Chen et al. (GenBank Accession No. A34914, 1995) or Devine et al. (GenBank Accession No. A38696, 1992) or Devault et al. (GenBank Accession No.A34786, 7-13-1990). This rejection is based upon the public availability of printed publications. Claims 5 and 9 of the instant application are drawn to an isolated polypeptide (P-glycoprotein or MDRP-1a) or fragment thereof which comprises at least one amino acid of a cynomologous P-glycoprotein selected from the group consisting of amino acids 12, 24, 30, 74, 78, 86, 89, 90, 91, 92, 95, 97, 99, 102, 103, 104, 185,324, 363, 518, 535, 650, 656, 659, 677, 730, 738, 742, 745,761,765,835,851,921,967, 1003, 1027, 1038, 1048, 1103, 1128, 1168 and 1277 of SEQ ID NO:2 or comprising amino acids 93, 94 and 95 of SEQ ID NO:4, wherein the P-glycoprotein is identical to a human P-glycoprotein except for the at

least one amino acid of a cynomologous P-glycoprotein. All the above references disclose such a polypeptide wherein said reference polypeptide comprises at least one of the above amino acids from either SEQ ID NO:2 or 4. Therefore, claims 5 and 9 are anticipated as written. (see enclosed sequence alignments).

Claims 5 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Sorrentino et al. (US 6933150, with priority date 5-27-1999) or Spalding et al. (US 6858774, with priority date 9-25-1998) or McDonough et al. (US 5837536, with priority date 1992). This rejection is based upon the public availability of patents granted to others. Claims 5 and 9 of the instant application are drawn to an isolated polypeptide (P-glycoprotein or MDRP-1a) or fragment thereof which comprises at least one amino acid of a cynomologous P-glycoprotein selected from the group consisting of amino acids 12, 24, 30, 74, 78, 86, 89, 90, 91, 92, 95, 97, 99, 102, 103, 104, 185,324, 363, 518, 535, 650, 656, 659, 677, 730, 738, 742,745, 761, 765, 835, 851, 921, 967, 1003, 1027, 1038, 1048, 1103, 1128, 1168 and 1277 of SEQ ID NO:2 or comprising amino acids 93, 94 and 95 of SEQ ID NO:4, wherein the P-glycoprotein is identical to a human P-glycoprotein except for the at least one amino acid of a cynomologous P-glycoprotein. All the above references disclose such a polypeptide wherein said reference polypeptide comprises at least one of the above amino acids from either SEQ ID NO:2 or 4. Therefore, claims 5 and 9 are anticipated as written. (see enclosed sequence alignments).

Claim 6 is rejected under 35 U.S.C. 102(e) as being anticipated by Sorrentino et al. (US 6933150, with priority date 5-27-1999) or Spalding et al. (US 6858774, with priority date 9-25-

1998). This rejection is based upon the public availability of patents granted to others. Claim 6 of the instant application is drawn to an isolated polypeptide (P-glycoprotein or MDRP-1a) or fragment thereof which comprises at least one amino acid of a cynomologous P-glycoprotein selected from the group consisting of amino acids 12, 24, 30, 74, 78, 86, 89, 90, 91, 92, 95, 97, 99, 102, 103, 104, 185,324, 363, 518, 535, 650, 656, 659, 677, 730, 738, 742, 745, 761, 765, 835, 851, 921, 967, 1003, 1027, 1038, 1048, 1103, 1128, 1168 and 1277 of SEQ ID NO:2 or comprising amino acids 93, 94 and 95 of SEQ ID NO:4, wherein the P-glycoprotein is identical to a human P-glycoprotein except for the at least one amino acid of a cynomologous P-glycoprotein and comprises the amino acid sequence of SEQ ID NO:5 or 6. All the above references disclose such a polypeptide wherein said reference polypeptide comprises at least one of the above amino acids from either SEQ ID NO:2 or 4 and has an amino acid sequence that is 100% identical to SEQ ID NO:5. Therefore, claim 6 is anticipated as written. (see enclosed sequence alignments).

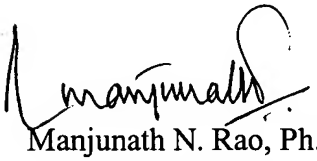
Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the receptionist whose telephone number is

571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

November 28, 2006